Efficacy of topical phenytoin on chemotherapy- induced oral mucositis; a pilot study

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Received 26 Sept 2009; Revised 28 Dec 2009; Accepted 5 Jan 2010

ABSTRACT

Background and the Purpose of the Study: Oral mucositis is one of the most common complications of malignancy chemotherapy. As yet, no absolute treatment has been demonstrated to be effective for chemotherapy- induced oral mucositis. This study evaluates the effectiveness of phenytoin mouthwash as a wound healing agent, on the basis of stimulating effects on fibroblast proliferation.

Materials and Methods: In this multicenter, randomized, placebo- controlled clinical trial; twelve patients received phenytoin mouthwash (0.5%) or placebo for about two weeks. Oral pain severity was scored on the daily basis using a VAS (visual analogue scale) of 10 centimeters. National Cancer Institute (NCI) scale was used to grade the intensity of mucositis. To determine the effect of treatment, a quality of life questionnaire, consisting of 35 queries, was filled out for all patients. Statistical analyses of data was performed using Mann- Whitney test.

Results: The average time for complete remission of mucositis in phenytoin- treated group was less than that of the placebo group. The quality of life improved dramatically in the phenytoin group with the healing process being more evident in the first week. Furthermore, reduction in the wound area was greater in the phenytoin group than controls at the end of the first week of treatment. Both groups eventually demonstrated reduction in pain intensity; however no statistically significant difference was observed between two groups.

Conclusion: Phenytoin mouthwash accelerated wound healing and resolution of mucositis and improved life quality impressively.

Keywords: Phenytoin, Mucositis, Chemotherapy

INTRODUCTION

Destruction of oral mucosa, known as oral mucositis, is a result of cancer therapy with chemotherapeutic agents which typically manifests as erythema, edema, athrophy or ulcerations of oral mucosa. The prevalence of oral mucositis after chemotherapy is 15- 40% (1). It can compromise a patient's ability to tolerate planned cancer therapy, and leads to missing or reducing doses and eventually a less successful prognosis. For patients being treated with the most common chemotherapy regimens for bone marrow transplant, the prevalence of oral mucositis may increase to 75-100%. In this group of patients, oral mucositis comprises one of the most debilitating aspects of cancer therapy. Oral mucositis, especially when severe, has a major impact on the quality of life and daily functioning of patients (2). It can present different levels of severity, ranging from a minor erythema to large and painful ulcers that limit basic oral functions such as swallowing, eating, drinking, and talking. In addition to direct complications (such as septicemia), oral mucositis leads indirectly to the elongation of hospitalization period and an increase in the treatment cost (1, 2).

A number of different strategies for the management of mucositis have been proposed including: debridement of oral lesions, oral decontamination, topical & systemic pain management, prophylaxis, and control of bleeding (1, 3). Different methods and medical agents have been developed to alleviate the symptoms and combat oral mucositis including mouthwash solutions such as alopurinol (4), chlorhexidine, diphenhydramine, aluminium hydroxide and pallifermin (5, 6). Unfortunately each of these agents only target limited and specific aspects of the condition and are ineffective on the other ones.

Phenytoin, an antiseizure medication, has been reported to promote wound healing when applied as a topical agent on skin and mucosal lesions (7) . It has been proven to be effective on acute and chronic lesions with various etiologies such as decubitus ulcers, leprosy ulcers, pressure sores, diabetic ulcers

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(8) , traumatic wounds, burns, epidermolysis bullosa (simplex type), aphthous ulceration, and oral lichen planus (9, 10) . Phenytoin promotes wound healing by a number of mechanisms including stimulation of fibroblast proliferation, facilitation of collagen deposition by inhibiting the activity of collagenase enzymes, and antibacterial activity. Furthermore, by stabilizing neural fiber membranes and reducing the inflammatory response, phenytoin contributes to the topical pain relief (9, 11) .

Since in chemotherapy, the submucosal tissue is targeted by stomatotoxic materials and fibroblasts apoptosis precedes the epithelial damage (12) , the ability of phenytoin to induce fibroblast proliferation and collagen deposition, makes a great contribution to the treatment of oral mucositis. Moreover, the side effects of topical phenytoin are rare and its systemic absorption is insignificant (9, 10) .Phenytoin appears to be a safe, effective, easy- to –use, and inexpensive treatment modality (9) . Various studies and reviews have been reported on the beneficial effects of phenytoin on the treatment of skin and soft tissue wounds and ulcers of various types. However, little attention has been paid to its role in the healing of oral lesions. Based on our research, so far, only one study has specifically investigated the effect of topical phenytoin on the healing process of oral lesions (aphthous stomatitis in particular) (13) .Therefore, areas of potential research that may improve the current knowledge and clinical management of oral mucositis by topical phenytoin is merited.

In the present study, the effectiveness of phenytoin mouthwash as an analgesic and wound healing agent on chemotherapy- induced oral mucositis have been assessed and compared with placebo.

MATERIAL AND METHODS

This study was designed as a randomized, placebo-controlled clinical trial, where the patients, the nurse who handed in the mouthwash (phenytoin and placebo) to the patients, and the clinician who examined the subjects and recorded the results, were all blind to the subject's assignment to trial groups. The study population consisted of patients undergoing chemotherapy process, due to various types of malignancies, from December of 2006 to May of 2007. Patients were recruited from oncology department of Taleghani Hospital, and Internal Medicine and oncology Wards of Naft Hospital in Tehran, Iran. The number of patients in treatment and control groups in each department was equalized (2 patients with solid tumors from departments of Internal Medicine, and 10 patients with blood malignancies from Oncology Department of Naft & Taleghani Hospitals). Patients were assigned to case & control groups randomly and separately at each department.

Sampling method was performed on a multi- central, non- probable (easy- to- access) basis. Data were collected by observation and interview. The inclusion criteria were as follows:

Patients undergoing chemotherapy without simultaneous radiation therapy; 2) Suffering from mucositis of grade 2 (erythema, edema, or painful lesions, but solid diet tolerated) or 3 (erythema, edema, and oral ulcers with need for intra- venous hydration) according to National Cancer Institute (NCI) classification (14) ; 3) Not being affected by systemic diseases including oral mucositis (such as connective tissue diseases and Sjogren syndrome), or interference with healing process of tissues (such as diabetes); 4) Not being a heavy smoker according to WHO definition; 5) Having informed consent of patients and their physicians, and no interference of this treatment with that of the primary disease/ cancer; 6) Absence of severe psychological disorders, such as major depression, which would interfere with the research process; 7) Patient's prognosis for at least 6 month is estimated.

Exclusion criteria: 1) Patient developing mucositis of grade 4 based on NCI grading scale; 2) Appearance of treatment side effects (such as allergy); 3) No cooperation or no tendency to continue the treatment process on behalf of the patient.

All patients with oral mucositis due to cancer therapy who met the inclusion criteria were randomly classified to two groups of treatment and placebo.

Two patients were uncooperative and excluded later during the investigation. The remaining 12 patients were examined for oral mucositis, and the severity of the condition was scored using the NCI scale. The oral mucosa was divided to 7 sites on the right and 7sites on the left (including: vestibular and buccal mucosa, gingivae, floor of the mouth & ventral surface of the tongue, margins & dorsal surface of the tongue, vestibular & labial mucosa, soft palate, and hard palate), and the score of mucositis was determined separately for each site.

These evaluations were performed at three intervals: prior to the start of the study, one and two weeks after beginning of the study. The date of treatment commencement and that of mucositis termination was recorded, and based on these dates duration of mucositis was calculated. Resolution of mucositis was considered when there was no evidence of mucositis of grade 2 or 3 at any site of the oral cavity.

Oral pain severity was reported on a daily basis using a visual analogue scale (VAS), which anchored with "no pain at all" and "the worst pain possible" at 0 and 10, respectively. Until the complete resolution of mucositis, patients' oral pain was recorded on a separate piece of paper daily, then measured with a fine ruler on a millimeter scale and finally transferred to the original data forms. This effort was made to make the measurements as independent as possible in a way that the patient would not rate his/her pain according to what he/she had recorded on the day(s) before. Furthermore, to evaluate the patients' quality of life, a persian translation of the standard questionnaire of life quality which had

Table 1. Patients' mucositis grade at three intervals

Mucositis Grade	at the start of study		after one week		after two weeks	
	case	control	case	control	case	control
0	0	0	1	0	6	1
1	0	0	5	1	0	3
2	2	1	0	4	0	2
3	4	5	0	1	0	0
average score[1]	6.0	7.0	3.9	9.1	4.0	9.0
z	0.638		2.704		2.708	
p	0.523		0.007		0.074	

1= Mann- Whitney Test

been validated in former studies (15) was used. The questionnaire consisted of 35 queries, was completed at the three aforementioned intervals. For the first 30 queries a Lickert- type scale was utilized permitting the patients to scale responses.

For each question 4 answers were considered. The responses: "absolutely not", "very little", "relatively high", and "very much", were assigned scores of 1, 2, 3, and 4 respectively. The first 16 questions were related to the oral signs and symptoms during the last week, and the next 14 queries were on private and social relations. The next 5 questions were designed in a "yes" or "no" format (score 2 and 1 respectively) to evaluate the general aspects such as weight changes, use of analgesics, and nutritional status. For every unanswered question a score of 1 was recorded. Therefore, the lowest and the highest possible score in the quality of life questionnaire were 35 and 130 respectively.

Phenytoin was prepared as an oral rinse at a concentration of 0.5% (Alborz Pharmaceutical Company, Tehran, Iran).The concentration of topical phenytoin creams, which are applied on skin lesions, is about 1%. Considering the greater mucosal absorption of phenytoin compared to its cutaneous absorption, the 0.5% concentration was chosen.

In order to minimize the burning effect of sodium phenytoin (13) as well as to maximize its therapeutic effect, half of the phenytoin used in the oral rinse was soluble sodium phenytoin salt and the other half was phenytoin powder.

The phenytoin and placebo solutions were prepared in the same color and containers. Administration was supervised by the department nurses four times a day and each time patients rinsed 10 ml of the solution in their mouths for 1 minute (to distribute evenly to all parts of the oral tissues) , and then expectorated (to minimize the systemic absorption). The treatment was continued until the complete healing of oral lesions or for a maximum of two weeks. In this study all the ethical criteria of the Research Deputy of "Shaheed Beheshti University of Medical Sciences" were met, and the informed consent form was signed by all patients.

Statistical analysis of data

All data was analyzed by SPSS 10.0 software. To describe the qualitative data, simple frequency was used; however, the frequency percentage was not expressed due to the limited number of samples. Means, standard deviations, ranges, and variation domains were determined to describe the quantitative data.

To analyze the nominal data (gender), Fisher's exact test was utilized. Non- parametric statistics such as Mann-Whitney test was used to analyze the ranking data (grade of lesion) and some of those quantitative data which didn't show normal distribution clearly (lesion duration and pain severity).

The quantitative data which were assessed at three intervals (grade of mucositis, and quality of life) were first compared with the mixed design using the variance analysis of repetitive quantities. The next relevant comparisons were drawn with the quality of life and the percentage of its changes, using the t- test. Type- 1 error (α) was considered to be equal to 0.05 and $p<\alpha$ was considered statistically significant.

RESULTS AND DISCUSSION

The phenytoin treatment group consisted of 3 males and 3 females. In the control group there were 2 males and 4 females ($p\sim1.000$; $X^2 = 0.343$). The mean age of the patients in groups of treatment and control were 38.8± 13.8 and 33.3± 14.8, respectively ($p= 0.520$; $t= 0.666$).

At the beginning of the study, there was no significant statistical difference between the two groups regarding mucositis severity. However, later at two intervals (one and two weeks after beginning of the study), mucositis severity in the treatment group was significantly lower than that of the control group (Table 1). In fact, after two weeks there was no trace of the lesions in any subjects of the treatment group. While the median duration of the lesions lasted for 4.5 days in the treatment group and it was in the range of 3-7 days, in the control group the least amount of time required for healing of the lesions was 6 days and in two of the subjects was even longer than 14 days. Based on Mann- Whitney test, the average score for the two groups of treatment and control were obtained to be 3.8 and 9.3 respectively, which

Table 2. Pain severity based on VAS (visual analogue scale, maximum of 10 centimeters) of the patients at different intervals

	At the start of study		after one week		after two weeks	
	case	**control**	**case**	**control**	**case**	**control**
Number of patients	6.0	6.0	6.0	6.0	6.0	6.0
Mean value	5.5	6.5	1.5	3.2	0	0.4
Standard Deviation	1.5	2.9	2.4	1.2	0	0.9
Average	5.5	5.5	0.5	3	0	0
Variance Domain	3-7	3-10	0-6	1-6	0-0	0-2
Average score [1,2]	6.2	6.8	5	8	5.5	6.6
z	0.328		1.467		1. 095	
p	0.743		0.142		0.273	

1= Mann- Whitney Test
2= parametric test (T- test) results (which corroborated with these results)

Table 3. Patients' quality of life at different intervals

	At the start of study		after one week		after two weeks	
	case	**control**	**case**	**control**	**case**	**control**
Number of patients	6.0	6.0	6.0	6.0	6.0	6.0
Mean value	70.2	71.8	51.7	66.8	45.5	53.7
Standard Deviation	13.8	16.0	4.8	12.8	3.7	7.9
Average	68.0	74.5	51.5	69.0	45.5	56.0
Variance Domain	57-96	45-87	47-60	45-82	41-50	40-61
t	0.193		2.718		1.906	
p	0.851		0.022		0.093	

demonstrated a significant statistical difference ($p=0.008$; $z=2.661$). The findings suggested that "mucositis duration" is a stronger, more creditable criterion compared to the two previous variables (i.e. grading of mucositis & pain severity). Since several sources had reported the maximum duration of mucositis to be two weeks (12) , in this study the mucositis treatment process was also followed up for about two weeks. If the follow-up was taking longer, the possibility of significant differences between the two groups would be higher. For example, one of the patients of the control group, who did not recover from mucositis at the end of the second week of study, stated that in previous periods he had experienced mucositis for about a month.

In both groups patients reported a drop in pain gradually ($p<0.001$; $F=41.789$) and no significant difference was observed between the two groups ($p=0.529$; $F=0.689$). Regarding pain intensity, at all intervals no significant difference was found between the two groups either (Table 2). Visual analogue scale (VAS) has been known as one of the most authentic and valuable criterion for measurement of the pain severity; and since it is determined by the patients it actually reflects their point of view, which is the main goal of the treatment. Unlike the "mucositis severity", which underwent a dramatic decrease in phenytoin treatment group compared to the control group, no significant difference was observed among patients of the two groups regarding the "pain severity". The reason is the relatively small number of the sample. Furthermore, the authenticity of VAS has been proved only for measurement of the pain severity at a single trial only. Meanwhile the concentration of the phenytoin mouthwash (0.5%) may be insufficient to allow the analgesic effects of the drug to appear or it may be even masked.

The patients' quality of life was also improved ($p=0.002$; $F=16.348$), and the difference between the two groups was found to be statistically significant ($p=0.028$; $F=6.219$) since life quality improvement in the treatment group was dramatically greater than the control group (Table 3). Although at the start of the study the difference between the life quality scores of the two groups was not statistically significant, after the first week the situation improved for the treatment group but after the second week, the difference between the two groups in terms of improvement of their life quality was not significant (Table 3). Since the patient's quality of life reflects the sum of the all therapeutic effects of the drug, improvement of life quality after 1 week in

the treatment group is indicative of the effectiveness of the treatment.

Although in this study serum levels of phenytoin in patients was not measured, but the systemic absorption of topical phenytoin is insignificant (8, 11).

In conclusion Phenytoin mouthwash accelerated healing of mucositis and improved life quality of patients of this study.

ACKNOWLEDGEMENTS

This study was supported by Research Deputy of Dental faculty, Shaheed Beheshti University of Medical Sciences, Tehran, Iran.

The authors are sincerely appreciated for contribution of: Dr.Togeh of Naft Hospital; Dr. Rezvani, of Taleghani Hospital; Dr.Zolfaghari, director of Alborz Pharmaceutical Company; Dr.Samiei and Dr.Sedaghat of Naft hospital .

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